Statin Therapy for Elevated hsCRP: What Are the Public Health Implications?

Paul M. Ridker, MD

One of the most difficult tasks all physicians face is staying abreast of biologic advances that fundamentally alter our understanding of disease and, in turn, our approaches to daily medical practice. Twenty years ago, we taught our medical students that atherosclerosis was simply a disorder of cholesterol metabolism. Today we teach a new generation of students that cholesterol is a major part of the story, but that inflammation also is a fundamental determinant of vascular risk. For example, in a recent meta-analysis of 54 prospective cohort studies, the magnitude of relative hazard for future vascular events associated with the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) was actually greater than that of either cholesterol or blood pressure.[1]

The fact that a patient is at risk for heart attack and stroke due to elevated levels of hsCRP does not, however, provide evidence to treat. That second step requires hard data that a therapy the patient would not otherwise have received provides clinical benefit. Twelve years ago we demonstrated that statin therapy not only reduces low-density lipoprotein cholesterol (LDL-C), but also reduces hsCRP.[2] In a series of subsequent studies, we and others went on to show that the relative benefits of statin therapy were maximized not only when LDL-C levels were reduced, but also when hsCRP levels were reduced.[3-6] To directly address the public health implications of this new biology, we then designed and conducted the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which was an investigator-initiated study directly testing whether or not statin therapy could lower vascular event rates among a group who otherwise would never be treated (because they had native LDL-C levels that were already low), but in whom risk was clearly elevated (because they had increased levels of inflammation as detected by hsCRP). The trial was funded by AstraZeneca, but this company played no role in the analysis of the trial data and had no access to unblinded trial data until after the fully independent JUPITER Steering Committee had submitted its results for publication.

In brief, the 18,000-participant JUPITER trial overwhelmingly confirmed (1) that those with elevated hsCRP are at substantially elevated vascular risk despite low LDL-C levels and low Framingham Risk Scores and (2) that in this setting rosuvastatin 20 mg compared with placebo reduced the risk of myocardial infarction by 55%, stroke by 48%, bypass surgery and revascularization by 46%, deep vein thrombosis by 43%, and total mortality by 20%.[7-9] These hard clinical benefits were statistically significant in all subgroups evaluated, including women, minorities, and the elderly, groups that in the past had been understudied in major trials. Overall, the 5-year number needed to treat (NNT) was 25, a value smaller than that already considered to be effective in primary prevention for those with hyperlipidemia and substantially more efficient that the comparable NNT value for the treatment of hypertension.

Further, independent academic economists have reported that the cost-effectiveness of the JUPITER approach is in the range of $25,000 to $30,000 per quality-adjusted life-year, and in many subgroups this approach is cost saving to society. In contrast to comments made by some authors not fully familiar with the JUPITER trial data, not only did the absolute risk of future vascular events increase with increasing hsCRP levels, but the absolute benefit of rosuvastatin also was greatest among those with the highest baseline hsCRP levels.[10]

On the basis of these data, the US Food and Drug Administration approved a new use for statin therapy among those with elevated hsCRP and 1 additional risk factor, and the Canadian Cardiovascular Society recently issued new national guidelines indicating that statin therapy should be offered to those at "intermediate risk" who have elevated levels of hsCRP, even if LDL-C levels are low.[11] These are evidence-based decisions based on hard, randomized trial data.

Diet, exercise, and smoking cessation remain the core interventions for all individuals at risk for heart disease. However, what the JUPITER trial data tell us is that even among those who do not smoke, who eat well, or who exercise regularly, there is a substantive risk of heart disease when hsCRP is elevated. Further, that residual risk can be cut by almost half with a safe, proven pharmacologic therapy.

According to analyses done by the independent JUPITER trial academic study statistician, imple-

www.ajmc.com
Full text and PDF

mentation of the screen-and-treat strategy prospectively tested in JUPITER could result in as many as 500,000 fewer major vascular events in the United States alone. Physicians who are up-to-date regarding new biologic principles and who have thoughtfully considered the totality of evidence regarding inflammation, hsCRP, and vascular risk know that public health recommendations from 40 years ago are outdated and must change if we are to improve outcomes for our patients.

Author Affiliation: From the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston, MA.

Funding Source: None.

Author Disclosures: Dr Ridker is the Principal Investigator for the investigator-initiated JUPITER trial, which was funded by AstraZeneca. He also is listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease.

Address correspondence to: Paul M. Ridker, MD, Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, 900 Commonwealth Ave East, Boston, MA 02215. E-mail: pridker@partners.org.

REFERENCES

1. The Emerging Risk Factors Collaboration; Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet.* 2010;375(9709):132-140.

2. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation.* 1998;98(9):839-844.

3. Ridker PM, Rifai N, Clearfield M, et al; Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med.* 2001;344(26):1959-1965.

4. Nissen SE, Tuzcu EM, Schoenhagen P, et al; Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med.* 2005;352(1):29-38.

5. Ridker PM, Cannon CP, Morrow D, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med.* 2005;352(1):20-28.

6. Morrow DA, de Lemos JA, Sabatine MS, et al. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation.* 2006;114(4):281-288.

7. Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359(21):2195-2207.

8. Glynn RJ, Danielson E, Fonseca FA, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med.* 2009;360(18):1851-1861.

9. Ridker PM, Danielson E, Fonseca FA, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet.* 2009;373(9670):1175-1182.

10. Ridker PM, MacFadyen J, Libby P, Glynn RJ. Relation of baseline high-sensitivity C-reactive protein level to cardiovascular outcomes with rosuvastatin in the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). *Am J Cardiol.* 2010;106(2):204-209.

11. Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult—2009 recommendations. *Can J Cardiol.* 2009;25(10):567-579.